Attorney Docket No. 147/50194

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:

Regina Schoemaker

Serial No.: 09/917,858 Group Art Unit: 1615

Filed: July 31, 2001 Examiner: Channavajjala, L.S.

For: USE OF MOXONIDINE FOR POSTMYOCARDIAL INFARCTION TREATMENT

DECLARATION UNDER 37 C.F.R. §1.132

Director of the U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Dr. Heinz Rupp, hereby declare as follows:

1. I am a citizen of the Federal Republic of Germany, residing at Baldinger Strasse, D-35033 Marburg, Germany.

2. I studied biochemistry at the University of Tuebingen in Tuebingen, Germany and received the degree of Doctor of Philosophy (Ph.D.) in biochemistry in 1975.

3. I have been engaged in the field of Cardiovascular Sciences since 1979, and my current title is Professor of Physiology in the Department of Internal Medicine and Cardiology at the Phillipps University of Marburg in Marburg, Germany.

4. I am the author or a co-author of over 130 scientific publications, the vast majority of which are directly related to cardiology and cardiac function.

5. I am a member of the Advisory Boards for the following Scientific Journals and Organizations:

- Journal of Experimental and Clinical Cardiology (1998-2003)
- Journal of Molecular and Cellular Cardiology (1994-2001)
- Molecular and Cellular Biochemistry (1987-2003)

6. I am a member of the following Professional Organizations:

- German Cardiology Society (1983-2003)
- International Society for Molecular Nutrition and Therapy (1992-2003), Secretary General

7. I am familiar with the invention described and claimed in the above-referenced patent application which is a method of treating postmyocardial infarction through administration of 4–chloro-5-[(4,5-dihydro-1H-imidazol-2-yl)amino]-6-methoxy-2-methylpyrimidine (hereinafter referred to as "moxonidine") or a physiologically acceptable acid addition salt thereof. I make this declaration in support of the patent application.

8. The term "myocardial infarction" refers to necrosis of heart muscle as a result of an interruption or reduction in the blood supply to the heart muscle. Following acute myocardial infarction, typical treatments may include analgesia, sedation, and administration of oxygen, nitroglycerin, aspirin, and/or atropine. Reperfusion of the heart muscle by either thrombolytic or fibrinolytic therapy within several hours following acute myocardial infarction is typically desirable in order to avoid further necrosis of heart muscle. In certain instances, further necrosis may lead to heart failure.

9. Myocardial infarction often leads to increased, chronic activation of the central sympathetic nervous system and increased catecholamine levels. Increased catecholamine levels are associated with numerous adverse events. [See Rupp H. and Jacob R., Excess Catecholamines and the Metabolic Syndrome: Should Central Imidazoline Receptors be a Therapeutic Target? *Medical Hypotheses*, Vol. 44, pages 217-225 (1995) (attached hereto as Appendix A)]. Persistent stimulation leads to a decrease in sensitivity to the stimulation, impairing the normal regulation of heart rate and contractile force. The increased catecholamine levels may also increase vascular tone and afterload of the heart and contribute to the development of cardiac hypertrophy.

10. Catecholamines can become oxidized to various adrenochromes and adrenolutins involving deleterious oxygen radicals. [See Rupp H., et al., Mechanisms of Cardiac Cell Damage Due to Catecholamines: Significance of Drugs Regulating Central Sympathetic Outflow, *Journal of Cardiovascular Pharmacology*, Vol. 24, Suppl. 1, pages S16-24 (1994) (attached hereto as Appendix B) and Dhalla K., Rupp H., et al., Mechanisms of Alterations in Cardiac Membrane Ca^{2+} Transport due to Excess Catecholamines, *Cardiovascular Drugs and Therapy*, Vol. 10, Suppl. 1, pages 231-238 (1996) (attached hereto as Appendix C)]. These oxygen radicals may induce oxidative stress and adversely affect various cellular and subcellular structures. [See Rupp, *Journal of Cardiovascular Pharmacology*, Vol. 24, Suppl. 1, pages S16-24 (1994) (Appendix B)]. For example, radicals derived from hydrogen peroxide have an inhibitory action on the signaling of the beta-adrenergic receptor pathway by changing the function of G_s proteins and the catalytic subunit of the adenylyl cyclase enzyme. [See Persad S., Rupp H., et al., Modification of Cardiac Beta-Adrenoceptor Mechanisms by H_2O_2, *American Journal of Physiology – Heart and Circulatory Physiology*, Vol. 274, pages H416-23 (1998) (attached hereto as Appendix D)].

11. As described in the above referenced patent application, the treatment method of the invention is specifically applicable to inhibit myocardial damage secondary to myocardial infarction, i.e., consequent damage which occurs subsequent to acute myocardial infarction. The invention relates to the unexpected finding that administration of moxonidine to rats subjected to surgically induced myocardial infarction yielded plasma catecholamine levels below levels exhibited in a negative control provided by sham operated rats. See Table 1 of the patent application (Table 1). This reduced catecholamine level is associated with a reduced heart rate, which was significantly lower that that of the sham operated rats. See Table 1.

12. The reduced plasma catecholamine levels and the associated reduced heart rate provide an unexpected and novel approach for selectively interfering with a major adverse result of myocardial infarction (chronic activation of the central sympathetic nervous system and increased catecholamine levels). These findings provide the basis for a novel therapy for the prevention of further myocardial damage to be initiated either acutely after myocardial infarction or post-myocardial infarction.

13. International Publication No. WO 97/46241 (the '241 application) (attached hereto as Appendix E) relates to the hemodynamic parameters associated with congestive heart failure, which is distinct from the general class of myocardial damage secondary to myocardial infarction. There is no information provided in the '241 application regarding the treatment or inhibition of myocardial damage secondary to myocardial infarction. Further, the '241 application does not teach or suggest administering moxonidine to inhibit myocardial damage secondary to myocardial infarction. While congestive heart failure may result from myocardial infarction, treatments for congestive

heart failure are not necessarily suitable as treatments to avoid or inhibit damage secondary to myocardial infarction. Congestive heart failure may be caused by a wide variety of mechanisms or conditions other than myocardial infarction, for example, coronary artery disease; hypertension; metabolic disorders such as thyroid disease, vitamin deficiency, and diabetes mellitus; exposure to toxins; cardiac amyloidosis; hemochromatosis; neuromuscular disease; collagen vascular disease; valvular heart disease; peripartum cardiomyopathy; high-output heart failure; arteriovenous fistula; severe anemia; paget's disease; chronic viral myocardial infection; autoimmune mechanisms; and genetic factors. Just as it would be improper to assume that a treatment for congestive heart failure is suitable for treating all of the foregoing mechanisms or conditions which may precede congestive heart failure, it is similarly improper to assume that the method of treating congestive heart failure taught in the '241 application would be proper or even beneficial in treating a postmyocardial infarction patient.

14. Congestive heart failure "may be defined as an inability of the heart to supply the metabolic demands of the periphery with sufficient blood for proper nutrition and waste removal." [See the '241 application, page 1, lines 17-20]. Treatment of congestive heart failure is targeted at improving the function of the heart, not inhibiting myocardial damage, as claimed in the claims of the present application.

15. Because the '241 application deals only with a treatment of congestive heart failure, and because treatments for congestive heart failure are only targeted at improving heart function, and cannot be assumed to be beneficial to inhibit damage secondary to myocardial infarction, the '241 application provides no teaching or suggestion to administer moxonidine to inhibit damage secondary to myocardial infarction. Further, the '241 application provides no motivation

for a person skilled in the art to try to inhibit myocardial damage by administering moxonidine following myocardial infarction.

16. The Lepran article, Effect of Moxonidine on Arrhythmias Induced by Coronary Artery Occlusion and Reperfusion, *Journal of Cardiovascular Pharmacology*, Vol. 24 (Suppl. 1), pages S9-S15 (1994) (attached hereto as Appendix F), similarly does not teach or suggest administering moxonidine to inhibit postmyocardial infarction damage, or to recover myocardial status. The Lepran article is limited to describing the effects of moxonidine pretreatment on arrhythmias or ventricular fibrillation induced by myocardial ischemia or reperfusion in an animal model. The notion that arrhythmias or ventricular fibrillation equates to "damage" as recited in the claims of the present application is incorrect because the damage recited in the claims is related to actual myocardial damage in a postmyocardial infarction patient. The arrhythmias or ventricular fibrillation discussed in the Lepran article represent abnormal heart operation, but not necessarily myocardial damage. Treatment to inhibit myocardial damage following myocardial infarction or to recover myocardial status is separate and distinct from treatment for arrhythmia or ventricular fibrillation.

17. The methods in the Lepran article rely on pretreatment with moxonidine in order to achieve results. In these methods, the moxonidine was administered before coronary ligation leading to either myocardial infarction or myocardial ischemia. The claims of the present application, however, relate to treatment of a patient after a myocardial infarction, by administration of moxonidine after a myocardial infarction. Because the methods in the Lepran article rely on pretreatment with moxonidine, the Lepran results are not useful for predicting what effect, if any, moxonidine might have on a postmyocardial

infarction patient. The authors of the Lepran article acknowledge this in their final paragraph, stating:

> In conclusion, moxonidine effectively reduced the incidence of arrhythmias during the acute phase of experimental myocardial infarction in conscious rats and during reperfusion after a brief period of myocardial ischemia in anesthetized rats. These results suggest that during chronic administration as an antihypertensive agent, moxonidine may also offer beneficial effects in the acute phase of an evolving myocardial infarction.

This clearly indicates that the authors understood their results suggest moxonidine may be useful if administered so as to be present during acute myocardial infarction. The results provide no suggestion or motivation to one skilled in the art that moxonidine administration following myocardial infarction might be beneficial in inhibiting damage, as is presently claimed. Therefore, the subject matter of the claims of the present application is not described by the Lepran article.

18. Based on my review of the present patent application, the references discussed above, and my general knowledge of the state of the art for myocardial infarction treatment, I conclude that no currently available therapy for postmyocardial infarction patients provides any suggestion or motivation to administer moxonidine to inhibit damage secondary to myocardial infarction or to provide myocardial recovery following myocardial infarction.

19. The damage inhibiting and myocardial recovery inducing benefits of the administration of moxonidine in postmyocardial infarction patients were

unexpected and surprising and could not have been expected or predicted based on any previously published literature of which I am aware.

20. All statements made herein of my own knowledge are true, and all statements made on information and belief are believed to be true, and further, these statements were made with the knowledge that willful false statements and the like, so made, are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the patent application or any patent issued thereon.

November 18, 2003
Date

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